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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/663,347	09/15/2003	Hartmut Luecke	66778-335	1577

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EXAMINER	
FERNANDEZ, SUSAN EMILY	
ART UNIT	**PAPER NUMBER**
1651	

DATE MAILED: 01/06/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/663,347	LUECKE ET AL.	
	Examiner	Art Unit	
	Susan E. Fernandez	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 December 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18* is/are pending in the application.

4a) Of the above claim(s) *1-4,7-10 and 13-18* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *5, 6, 11, and 12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1)☒ Notice of References Cited (PTO-892)

2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

3)☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.

4)☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.

5)☐ Notice of Informal Patent Application (PTO-152)

6)☐ Other: _____.

DETAILED ACTION

The preliminary amendments filed February 19, 2004 and December 10, 2004, has been received and filed.

Claims 1-18 are pending.

Election/Restrictions

Applicant's election without traverse of Group III, claims 5, 6, 11 and 12 in the reply filed on December 10, 2004 is acknowledged.

Claims 1-4, 7-10 and 13-18 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected inventions, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on December 10, 2004.

Claims 5, 6, 11 and 12 are examined on the merits to the extent they read on the elected subject matter.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 11 and 12 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. Atomic coordinates are information and are not compositions of matter though they do describe protein crystalline complexes.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 5 and 6 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention.

Claims 5 and 6 are drawn to a crystalline complex *T. foetus* IMPDH in complex with ribavirin or ribavirin and mycophenolic acid. However, as noted on page 44 (lines 7-11 and lines 28-29) and Table 9 (page 492), the crystalline structures are actually of *T. foetus* IMPDH in complex with ribavirin monophosphate (RMP) or RMP and mycophenolic acid (MPA).

More specifically, the specification teaches the crystallization of *T. foetus* IMPDH of SEQ ID NO:2 in complex with RMP having the space Group P432 with cell unit dimensions a = b = c = 154.7 Å, and $\alpha = \beta = \gamma = 90°$. It also teaches the crystallization of *T. foetus* IMPDH of SEQ ID NO:1 in complex with RMP and MPA having the space Group P432 with cell unit dimensions a = b = c = 155.1 Å, and $\alpha = \beta = \gamma = 90°$. Both sets of complexes were crystallized under the conditions described in the specification (page 52, lines 29-31 and page 53, lines 1-8). There is no disclosure of any particular teaching on how to change the crystallization conditions to obtain any protein crystals of IMPDH in complex with ribavirin, ribavirin+MPA, RMP, or RMP+MPA with any change in the protein sequence or in any other crystal form.

The specification also fails to describe additional representative species of these crystals by any identifying structural characteristics or properties other than the cell dimension, for which no predictability of structure is apparent. Given this lack of additional representative species as encompassed by the claims, the claimed invention is not sufficiently described, in such full, clear, concise, and exact terms that a skilled artisan would recognize applicants were in possession of the claimed invention.

Regarding undue experimentation, *In re Wands*, 8 USPQ2d 1400, at 1404 (Fed. Cir. 1988) states:

> Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in *Ex parte Forman*. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. (Citations omitted).

The nature and breadth of the claimed inventions encompasses any crystal of *T. foetus* IMPDH in complex with ribavirin or ribavirin+MPA. The specification provides guidance and examples in the form of an assay to obtain the IMPDH proteins of SEQ ID NO:1 and SEQ ID NO:2, crystallize the protein under the conditions described in the specification ((page 52, lines 29-31 and page 53, lines 1-8), and characterize the crystalline complexes of *T.foetus* IMPDH with RMP or RMP+MPA through x-ray diffraction.

While molecular biological techniques and genetic manipulation to make any IMPDH protein having any amino acid sequence are known in the prior art and the skill of the artisan are well developed, knowledge regarding the crystallization conditions to obtain a suitable crystal for structure determination by the x-ray diffraction method is lacking. Thus, searching crystallization conditions for any IMPDH protein is well outside the realm of routine

experimentation and predictability of success in the art is extremely low. The amount of experimentation to identify appropriate crystallization conditions is enormous. Applicants should be reminded that growing protein crystals to a suitable size that diffracts x-ray is not amenable to scientific investigation. It relies mostly on trial and error. A minor change in an amino acid sequence such as a conservative mutation may have a profound effect on the crystallizability of a protein under given crystallization conditions. In many instances, a crystal can be obtained, but it diffracts x-ray poorly. Finally, the formation of a crystalline complex of IMPDH bound to RMP or RMP+MPA is highly unpredictable.

Due to the large quantity of experimentation necessary to generate crystalline structures of IMPDH complexes with ribavirin or ribavirin and MPA appropriate for x-ray diffraction, the lack of direction/guidance presented in the specification regarding exact crystallization conditions for all complexes of IMPDH+ribavirin or IMPDH+ribavirin+MPA and the amino acid sequences which are being crystallized, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of amino acid sequence on protein crystallization, and the absence of atomic coordinate tables of the claimed inventions (complexes consisting of ribavirin rather than RMP), undue experimentation would be required of the skilled artisan to make the claimed invention in its full scope.

Claims 5 and 6 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant

art that the inventors, at the time the application was filed, had possession of the claimed invention.

The specification discloses the crystalline complexes of *T. foetus* IMPDH of SEQ ID NO: 2 bound to RMP and *T. foetus* IMPDH of SEQ ID NO:1 bound to RMP+MPA. However, claims 5 and 6 encompass any *T. foetus* IMPDH bound to ribavirin or ribavirin and MPA. To provide evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, there is no identification, description of production, or description of use of any other *T. foetus* IMPDH proteins of sequences other than SEQ ID NO:1 and SEQ ID NO:2. Furthermore, no description is provided for the binding of ribavirin to IMPDH (rather than RMP), nor are any atomic coordinates given us IMPDH bound to ribavirin.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of *the invention*." The invention is, for purposes of the "written description" inquiry, *whatever is now claimed.* (See page 1117). The specification does not "clearly allow person of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116).

With the exception of the IMPDH proteins set forth in SEQ ID NO:1 and SEQ ID NO:2, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of polypeptides, regardless of the complexity or simplicity of the method of isolation. Furthermore,

the artisan cannot envision all permutations by which ribavirin alone or together with MPA may bind with *T. foetus* IMPDH, especially considering that not one example is provided of such complexes. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it or obtaining appropriate complexes. The proteins and complexes themselves are required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

Therefore, only crystalline complexes comprising isolated polypeptides of the amino acid sequences set forth in SEQ ID NO:1 and SEQ ID NO:2 and RMP or RMP+MPA, but not the full breadth of the claims meet the written description provision of 35 U.S.C. §112, first paragraph. Applicants are reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Susan E. Fernandez whose telephone number is (571) 272-3444. The examiner can normally be reached on Mon-Fri 8:30 am - 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mike Wityshyn can be reached on (571) 272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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sef

FRANCISCO PRATS
PRIMARY EXAMINER